Pendimethalin Exposure and Cancer Incidence Among Pesticide Applicators

Lifang Hou, Won Jin Lee,*§ Jennifer Rusiecki,* Jane A. Hoppin,† Aaron Blair,* Matthew R. Bonner,* Jay H. Lubin,‡ Claudine Samanic,* Dale P. Sandler,† Mustafa Dosemeci,* and Michael C. R. Alavanja**

Background: Pendimethalin, a widely used herbicide, has been classified as a group C possible human carcinogen by the U.S. Environmental Protection Agency. We evaluated the incidence of cancer in relation to reported pendimethelin use among pesticide applicators in the Agricultural Health Study, a prospective cohort of licensed pesticide applicators in Iowa and North Carolina.

Methods: Information on pesticide use came from two questionnaires (enrollment and take-home). The present analysis includes 9089 pendimethalin-exposed and 15,285 nonpendimethalin-exposed pesticide applicators with complete information on pendimethalin use and covariates from a take-home questionnaire. We conducted Poisson regression analyses to evaluate the association of pendimethalin exposure with cancer incidence (mean follow-up = 7.5 years) using two exposure metrics: tertiles of lifetime days of exposure and tertiles of intensity-weighted lifetime days of exposure.

Results: Overall cancer incidence did not increase with increasing lifetime pendimethalin use, and there was no clear evidence of an association between pendimethalin use and risks for specific cancers. The risk for rectal cancer rose with increasing lifetime pendimethalin exposure when using nonexposed as the reference (rate ratio = 4.3; 95% confidence interval = 1.5–12.7 for the highest exposed subjects; P for trend = 0.007), but the association was attenuated when using the low exposed as the referent group (P for trend = 0.08). Similar patterns for rectal cancer were observed when using intensity-weighted exposure-days. The number of rectal cancer cases among the pendimethalin-exposed was small (n = 19). There was some evidence for an elevated risk for lung cancer, but the excess occurred only in the highest exposure category for lifetime pendimethalin exposure. The trends for lung cancer risk were inconsistent for different exposure metrics.

Conclusions: We did not find a clear association of lifetime pendimethalin exposure either with overall cancer incidence or with specific cancer sites.

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Pendimethalin (*N*-[1-ethylpropyl]-2,6-dinitro-3,4-xylidine), a dinitroaniline, is a widely used herbicide for control of annual grasses and certain broadleaf weeds in commercial crops.[1] In 1997, 2 to 4 million pounds of pendimethalin were used, increasing to 3 to 5 million pounds in 1999.[2]Pendimethalin is available as an emulsifiable concentrate, wettable powder, or dispersible granular formulations.[3,4]

The U.S. Environmental Protection Agency (EPA) classifies pendimethalin as a "slightly toxic" compound (toxicity class III) and a possible human carcinogen (group C).[5] The U.S. EPA has reported that pendimethalin causes thyroid follicular cell adenomas in rats.[5]

The Agricultural Health Study in Iowa and North Carolina was designed to investigate the possible links between a wide variety of agricultural and lifestyle factors and risks of cancers, as well as other chronic diseases, among farmers and commercial pesticide applicators.[6] With the exception of a recent analysis from the Agricultural Health Study, which suggested a possible association between pendimethalin exposure and lung cancer risk,[7] there have been no epidemiologic studies of pendimethalin exposure in relation to diseases. We were, therefore, motivated to assess the possible relationship between pendimethalin use and the incidence of all cancers.

METHODS

Cohort Enrollment and Follow-Up

The Agricultural Health Study is a prospective cohort of 57,311 applicators licensed to apply restricted-use pesticides and 32,347 spouses of private applicators from Iowa and North Carolina.[6] Recruitment of applicators began in December 1993 and continued until December 1997. Infor-

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From the *Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD; the †Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC; the ‡Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD; and the §Department of Preventive Medicine, College of Medicine, Korea University, Seoul, South Korea.

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Correspondence: Michael C. R. Alavanja, 6120 Executive Blvd. EPS 8000, Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20852. E-mail: Alavanjm@mail.nih.gov.

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mation on full name, sex, date of birth, and Social Security Number provided by study participants at enrollment were used to link cohort members to cancer registry files in Iowa and North Carolina for cancer incidence identification and to the state death registries and the National Death Index to ascertain vital status. Incident cancers from date of enrollment (from 1993–1997) through December 31, 2002, were identified and coded according to the *International Classification of Diseases for Oncology* (ICD-2-O).[8] A self-administered enrollment questionnaire collected comprehensive exposure data, including use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, smoking history, alcohol consumption, cancer history of first-degree relatives, and basic demographics,[9] on 22 pesticides and information on ever/never use for 28 additional pesticides, including pendimethalin. An additional takehome questionnaire included more detailed questions on lifetime days, use of personal protective equipment, application methods, pesticide mixing, and equipment repair for the 28 additional pesticides for which only ever/never use was obtained in the enrollment questionnaire. Both the enrollment and takehome questionnaires are available on the web at www.aghealth.org. Approximately 40% of the cohort returned the takehome questionnaire; individuals who did or did not complete this questionnaire were similar with regard to demographic, pesticide use, and medical characteristics.[10] We censored person-years for individuals who had moved out of either Iowa or North Carolina in the year they departed. The mean duration of follow-up is 7.5 years, and 2666 incident cases of cancer were identified. A total of 407 first primary incident cancers occurred among these 9089 participants who completed the takehome questionnaire (Agricultural Health Study Data Release Version 0412.01).

Exposure Assessment

Estimates of lifetime exposure-days of pendimethalin were calculated from the number of years applied and the frequency of application using the midpoints of the questionnaire category (ie, years of use × days per year). Lifetime exposure-days were grouped into tertiles based on the distribution among all cancer cases combined. The pendimethalin categories for the tertiles were <8.75, 8.75–38.75, and >38.75 cumulative lifetime exposure-days.

We also used the Agricultural Health Study (AHS) exposure-intensity algorithm, which has been described elsewhere.[11] This algorithm was based on the following formula: intensity level = (mixing status + application method + equipment repair status) × personal protective equipment use. Scores assigned to each component of the intensity algorithm were weighted to reflect intensity of exposure as described in the literature. Mixing status had three levels (never mixed, personally mixed less than 50% of the time, and personally mixing more than 50% of the time). Application method had six levels (never applied, use of aerial–aircraft or distribution of tablets, application in furrow, use of boom on tractor, use of backpack, and use of hand spray). Equipment repair status had two levels (not repaired or repaired). Personal protective equipment had eight levels based on various types of equipment used while applying pesticides.[11] Intensity-weighted lifetime exposure-days were constructed by multiplying lifetime exposure-days by exposure intensity level (ie, years of use × days per year × intensity level),[11] and the cut points for tertiles were <54.8, 54.8–232.5, and >232.5 intensity-adjusted exposure-days.

Data Analysis

We carried out a preliminary analysis in the entire cohort comparing cancer incidence rates between applicators who ever (n = 27,818) and never (n = 23,298) used pendimethalin (data not shown). The results reported here are restricted to the subjects who returned the takehome questionnaire, including 15,285 subjects who reported no lifetime pendimethalin exposure and 9089 subjects who provided detailed information on lifetime pendimethalin exposure. We excluded subjects (n = 16) who did not provide complete information on pendimethalin application (ie, missing information on one or more of the followings: mixing status, application method, equipment repair status, and personal protective equipment use) from the analysis of intensity-weighted lifetime pendimethalin exposure.

Poisson regression was used to evaluate the effect of pendimethalin exposure on cancer incidence. We adjusted for potential confounding factors, including age at enrollment (<40, 40–49, 50–59, ≥60 years), sex, education (≤high school graduate, >high school), cigarette smoking history (never/low/high using the median value of pack-years [11.25 packs/y] among smokers to classify low and high categories), alcohol drinking during past 12 months (yes/no), family history of cancer in first-degree relatives (yes/no), state (Iowa/North Carolina), and the five pesticides with which pendimethalin was most highly correlated (ziram, r = 0.97; dieldrin, r = 0.92; butylate r = 0.70; chlorimuron ethyl r = 0.71; and metribuzin, r = 0.78 by Pearson correlation coefficient, using lifetime exposure-days). To evaluate whether the effect of pendimethalin might be due to chemicals with highly correlated use patterns (ie, ziram and dieldrin), we also ran the model by excluding subjects who were also exposed to ziram or dieldrin. Exposure levels for these five pesticides were categorized into groups of never, low, and high using median of their cumulative lifetime exposure-days. For analyses of lung cancer incidence, we additionally controlled for smoking status (current, former, and never), smoking duration, pack-years smoked, and exposure to three other pesticides (metolachlor, chlorpyrifos, and diazinon) that were associated with lung cancer risk in a previous study of the AHS.[7] In case there were unmeasured differences in baseline characteristics between applicators never exposed to pendimethalin and those with low pendimethalin exposure, which may potentially confound associations, we calculated rate ratios (RRs) and associated 95% confidence intervals (CIs) using both nonexposed and low-exposed groups as the referent group. The highest tertile of pendimethalin exposure was further split in half whenever there were at least 10 exposed cases, using lifetime pendimethalin exposure-days, to examine effects at more extreme levels of exposure. To consider disease latency, we repeated analyses by reclassifying subjects who started using pendimethalin after 1990 as nonpendimethalin-exposed. The latency analysis was limited

somewhat because we have information only on the starting decade of pendimethalin use.

Tests for trend were performed by assessing the significance of a linear effect among median values for each category in the logistic regression model.[12] Analyses were performed using the STATA program (version 8.0; Stata Corp., College Station, TX).

RESULTS

Using data for the entire cohort, we found no increased risk for any cancers when we compared pesticide applicators who reported ever versus never personally mixing or applying pendimethalin (data not shown).

Among subjects who returned a takehome questionnaire (n = 9089), the majority of the pendimethalin-exposed cohort consisted of male private applicators residing in Iowa (Table 1). The consumption of alcohol and cigarettes differed between the pendimethalin-exposed and -nonexposed groups. Pendimethalin-exposed applicators were more heavily exposed to all pesticides than nonpendimethalin users.

For cancer incidence rates, we report results for all cancers combined and tumor sites for which there were at least 15 exposed cases in Tables 2 and 3. We found no increase in overall cancer incidence with increasing lifetime pendimethalin exposure (Table 2). The RR for lung cancer was elevated among subjects in the upper half of the highest tertile of lifetime pendimethalin exposure-days when compared with either the unexposed (RR = 2.4; 95% CI = 1.1–5.3) or the low-exposed pendimethalin applicators (3.5; 1.2–10.8), but patterns of RRs were not monotonic with lifetime exposure-days (Table 2). However, when using intensity-weighted exposure metrics, we did not observe elevated RRs for lung cancer among subjects in the upper half of the highest tertile using either the nonexposed (1.1; 0.5–2.6) or low-exposed (1.1; 0.4–3.3) group as the referent. The risk for colorectal cancer was not associated with increasing pendimethalin exposure (for the highest exposed subjects, RR = 1.0; 95% CI = 0.3–3.4 when using the nonexposed as the referent group, or RR = 1.0; 0.2–4.4 when using the low-exposed as the referent group). We also evaluated risks for colon and rectal cancers separately. Based on small numbers (n = 40), there was an elevated risk of rectal cancer among subjects with the highest lifetime pendimethalin exposure-days compared with the nonexposed group (4.3; 1.5–12.7); a similar pattern was observed (4.4; 0.8–24.0) when using the low-exposed group as the referent. In contrast, there was no increase in risk for colon cancer associated with pendimethalin use. Prostate cancer, the most common tumor in the AHS cohort (1060 cases in the entire cohort and 169 among pendimethalin applicators), was not associated with pendimethalin use. Pendimethalin exposure was not associated with risk of all lymphohematopoietic cancers, melanoma, or non-Hodgkin lymphoma.

For intensity-weighted exposure-days, we observed no elevation in risk for all cancers using either the non- or low-pendimethalin-exposed group as the referent (Table 3). No increased RRs for lung cancer were observed using either referent group. An increased risk for rectal cancer was found comparing subjects in the highest tertile with the nonpendimethalin exposed applicators (RR = 3.6; 95% CI = 1.2–11.3; *P* for trend = 0.02), whereas no clear pattern of RRs was observed when using the low-exposed group as the referent (2.9; 0.5–16.7; *P* for trend = 0.23). We do not present the results for other cancer sites that were also reported in Table 2 because none showed altered risks by intensity-weighted pendimethalin exposure.

Analyses taking into account disease latency (by reclassifying applicators who started using pendimethalin after

TABLE 1. Selected Characteristics of Study Subjects by Pendimethalin-Exposure Status Among Pesticide Applicators in Agricultural Health Study, 1993–2002

		Exposed	
Characteristics	**Nonexposed (n = 15,285) %**	**Low-Exposed (n = 3654) %**	**High-Exposed† (n = 5435) %**
Age (years)			
<40	25	24	34
40–49	25	28	30
50–59	22	24	21
≥60	28	24	15
Sex			
Male	96	99	99
Female	4	1	1
State of residence			
Iowa	69	77	64
North Carolina	31	23	36
Applicator type‡			
Private	92	95	83
Commercial	8	5	17
Smoking history			
Never	56	56	52
Low (<12 pack-years)	22	22	23
High (≥12 pack-years)	22	22	25
Alcohol consumption			
Never	36	31	29
Ever	64	69	71
Education			
High school or less	57	56	54
Greater than high school	43	44	46
Family history of cancer			
No	56	56	58
Yes	44	44	42
All pesticide exposure§			
No	1	0	0
Low	36	23	13
Medium	35	39	31
High	28	38	56

*Including subjects in tertile 1 of lifetime pendimethalin exposure-days.
†Including subjects in tertiles 2 and 3 of lifetime pendimethalin exposure-days.
‡The term "private applicators" refers primarily to individual farmers and "commercial" refers to professional pesticide applicators in Iowa.
§Cumulative lifetime exposure-days to all pesticide among pendimethalin applicators.

TABLE 2. Rate Ratios* for Selected Cancers by Lifetime Exposure-Days to Pendimethalin†

Cancers	No. of Cases	Pendimethalin Exposure: Nonexposed Referent RR	(95% CI)	Pendimethalin Exposure: Low-Exposed Referent RR	(95% CI)
All cancers combined					
Nonexposed‡	907	1.0			
Exposed	407				
T1	164	0.8	(0.7–1.1)	1.0	
T2	101	1.0	(0.8–1.4)	1.2	(0.8–1.7)
T3 (lower half)	74	0.8	(0.6–1.2)	0.9	(0.6–1.4)
T3 (upper half)	68	1.3	(0.9–1.9)	1.5	(0.9–2.7)
P for trend		0.83		0.28	
Lung§					
Nonexposed‡	82	1.0			
Exposed	34				
T1	9	0.8	(0.4–1.6)	1.0	
T2	7	1.1	(0.5–2.5)	1.5	(0.5–4.3)
T3 (lower half)	7	0.8	(0.3–1.9)	1.1	(0.3–3.4)
T3 (upper half)	11	2.4	(1.1–5.3)	3.5	(1.2–10.8)
P for trend		0.29		0.06	
Colorectal					
Nonexposed‡	97				
Exposed	50				
T1	17	0.7	(0.3–1.6)		
T2	12	1.4	(0.6–3.4)	1.7	(0.5–5.5)
T3 (lower half)	12	1.3	(0.5–3.2)	1.5	(0.5–4.8)
T3 (upper half)	9	1.0	(0.3–3.4)	1.0	(0.2–4.4)
P for trend		0.7		0.9	
Colon					
Nonexposed‡	76	1.0			
Exposed	31				
T1	11	0.6	(0.2–1.6)	1.0	
T2	8	0.8	(0.3–2.8)	0.9	(0.6–4.5)
T3 (lower half)	6	0.5	(0.1–2.2)	0.5	(0.1–3.1)
T3 (upper half)	6	0.4	(0.05–3.2)	0.3	(0.02–3.0)
P for trend		0.20		0.25	
Rectum					
Nonexposed‡	21	1.0			
Exposed	19				
T1	6	0.9	(0.2–3.9)	1.0	
T2	4	2.6	(0.7–9.6)	2.9	(0.5–17.8)
T3	9	4.3	(1.5–12.7)	4.4	(0.8–24.0)
P for trend		0.007		0.08	
Prostate					
Nonexposed‡	392	1.0			
Exposed	169				
T1	80	1.1	(0.8–1.6)	1.0	
T2	39	0.9	(0.5–1.5)	0.8	(0.4–1.5)
T3 (lower half)	28	1.0	(0.5–1.6)	0.9	(0.5–1.6)
T3 (upper half)	22	1.0	(0.5–2.1)	1.0	(0.4–2.2)
P for trend		0.90		0.78	
Melanoma					
Nonexposed‡	31	1.0			
Exposed	19				
T1	9	1.2	(0.5–2.8)	1.0	
T2	4	0.7	(0.2–3.0)	0.5	(0.1–2.6)
T3	6	1.3	(0.4–3.8)	0.9	(0.2–3.2)
P for trend		0.80		0.77	
All lymphohematopoietic cancers					
Nonexposed‡	78	1.0			
Exposed	39				
T1	16	0.8	(0.4–1.6)	1.0	
T2	13	1.4	(0.7–2.8)	1.6	(0.6–3.9)
T3	10	1.1	(0.5–2.3)	1.2	(0.5–3.0)
P for trend		0.70		0.73	
Non-Hodgkin lymphoma					
Nonexposed‡	28	1.0			
Exposed	20				
T1	6	0.8	(0.3–2.5)	1.0	
T2	9	2.6	(0.9–6.7)	2.5	(0.7–9.3)
T3	5	1.6	(0.5–4.5)	1.4	(0.3–5.8)
P for trend		0.18		0.64	

*Rate ratio adjusted for age, sex, alcohol, smoking, education, family history of cancer, enrollment year, state and the five pesticides most highly correlated with pendimethalin (ziram, r = 0.97; dieldrin, r = 0.92; butylate, r = 0.70; chlorimuron ethyl, r = 0.71; and metribuzin, r = 0.78).

†Lifetime exposure-days = years of use x days per year. The cut points for tertile 1, tertile 2, tertile, 3–lower, and tertile 3–upper of lifetime exposure-days are ≤8.75, 8.76–38.75, 38.75–116, and >116.

‡Reference category.

§Rate ratio were also adjusted for different smoking variables, including duration, pack/yr, and status of smoking.

1990 to the nonexposed group) did not reveal meaningful changes in the results (data not shown). Results without adjustment for the five most highly correlated pesticides were also similar. Excluding subjects who were also exposed to two extremely highly correlated pesticides (ie, ziram and dieldrin) from the model changed the results only slightly.

DISCUSSION

We found no increase in overall cancer incidence with increasing lifetime pendimethalin use, and no clear evidence of increased risks for any specific cancer sites. The increased risks for lung cancer did not display a monotonic exposure–response pattern and are inconsistent for different exposure metrics. The rising risk for rectal cancer was more interesting, although based on small numbers.

Only a few studies of the mutagenicity and carcinogenicity of pendimethalin have been carried out. Generally, these studies showed no clear evidence for mutagenic or carcinogenic effects of pendimethalin either in vivo or in

TABLE 3. Rate Ratios* for Selected Cancers by Intensity-Weighted Lifetime Exposure-Days to Pendimethalin†

		Pendimethalin Exposure			
		Nonexposed Referent		Low-Exposed Referent	
Cancers	No. of Cases	RR	(95% CI)	RR	(95% CI)
All cancers combined					
Nonexposed‡	907	1.0			
Exposed	391				
T1	132	0.9	(0.7–1.2)	1.0	
T2	128	0.9	(0.7–1.2)	1.0	(0.7–1.4)
T3 (lower half)	65	1.0	(0.7–1.4)	1.0	(0.6–1.6)
T3 (upper half)	66	1.0	(0.7–1.5)	1.0	(0.7–1.6)
P for trend		0.86		0.85	
Lung§					
Nonexposed‡	82	1.0			
Exposed	33				
T1	9	1.0	(0.5–2.2)	1.0	
T2	9	0.9	(0.5–1.9)	1.0	(0.4–2.5)
T3 (lower half)	6	0.9	(0.3–2.6)	0.9	(0.3–3.2)
T3 (upper half)	9	1.1	(0.5–2.6)	1.1	(0.4–3.3)
P for trend		0.94		0.84	
Rectum					
Nonexposed‡	21	1.0			
Exposed	18				
T1	6	1.1	(0.2–4.8)	1.0	
T2	5	2.5	(0.8–7.8)	2.1	(0.4–12.1)
T3	7	3.6	(1.2–11.3)	2.9	(0.5–16.7)
P for trend		0.02			0.23

*Rate ratio adjusted for age, sex, alcohol, smoking, education, family history of cancer, enrollment year, state and the five pesticides most highly correlated with pendimethalin (ziram, r = 0.97; dieldrin, r = 0.92; butylate, r = 0.70; chlorimuron ethyl, r = 0.71; and metribuzin, r = 0.78).

†Intensity-weighted lifetime exposure-days = years of use x days per year, the cut points for tertiles 1, tertile 2, tertile 3–lower, and tertile 3–upper are ≤54.8, 54.81–232.5, 232.5–539.4, and >539.4.

‡Reference category.

§Rate ratio were also adjusted for different smoking variables, including duration, pack/yr, and status of smoking.

vitro.[13] However, most recently, the U.S. EPA found that pendimethalin caused thyroid follicular cell adenomas in rats[5] and concluded that pendimethalin is a possible human carcinogen. In our study, the association between the incidence of rectal cancer and pendimethalin use among pesticide applicators occurred with both lifetime exposure-days and intensity-weighted lifetime exposure-days. Although, to date, no other studies could specifically focus on pendimethalin exposure and rectal cancer, some studies have investigated the effect of overall pesticides on rectal and colon cancer.[14–20] Observations for rectal cancer risk have been inconsistent,[14–20] with three of these studies reporting an increased risk with increasing overall pesticide use[14–16] and four showing no association.[17–20] The studies showing an association between rectal cancer and possible pesticide exposure reported no elevated risk for colon cancer. The observed differences in risks between colon and rectal cancers in our study and other studies[14–16] suggest different etiologies for these two cancer sites, as has been suggested previously.[21,22] Because of small number of rectal cancer cases (21 nonexposed and 19 exposed cases) and the absence of experimental evidence, this may be a chance finding.

The evidence for an increase in lung cancer risk among subjects with increasing pendimethalin exposure is inconclusive and based on elevated RRs only among subjects in the upper half of the top tertile using the lifetime-days exposure metric. The findings for lung cancer risk in the present study were weaker than those reported in the previous Agricultural Health Study analysis.[7] These differences are largely due to different exposure cut points (tertiles were based on all cancer cases in the current study,[7] whereas tertiles were based only on lung cancer cases in the previous one). In addition, adjusting for different confounders in these two analyses created small differences in the results.

Several limitations of this study are noteworthy. The intensity algorithms in this study were based on a literature review and not on direct measurements of exposure made within the study cohort. These weighting factors heavily emphasize dermal absorption over inhalation and other exposure routes. Furthermore, some subjects may have had inaccurate recall of pesticide use, thereby introducing exposure misclassification. For instance, in the present study, a few subjects (n = 19) who reported no overall pesticide use did report some pendimethalin exposure. Our sensitivity analyses showed no meaningful changes in the results when we either excluded these subjects or reclassified them as nonexposed, suggesting that classification of those subjects in the pendimethalin-exposed group did not affect our conclusions. A previous study showed that recall of pesticide use by the Agricultural Health Study cohort is comparable to the recall of other variables such as diet and alcohol consumption, which have been successfully used by epidemiologists in other studies.[23] Also, applicators in our study provided plausible information on dates of use of specific pesticides when compared with external data on pesticide registrations.[24] A possible error in exposure assessment introduced into this prospective study would most likely lead to nondifferential misclassification that would reduce any true excesses, thereby diminishing real exposure–response relationships. Most applicators used numerous pesticides, and some of these pesticides were highly correlated with pendimethalin exposure. We identified the five most correlated pesticides (correlation coefficients from 0.70 to 0.97) and adjusted for them in the final model. Results from the analyses by excluding either all five highly pendimethalin-correlated pesticides or only two most highly correlated ones (ie, ziram and dieldrin) from the final model did not show meaningful differences. Adjusting for all pesticide applications also did not significantly change the risk estimates. The relatively small number of cancer cases limited our ability to perform stratified analyses by smoking status, histologic type, and other conditions and exposures. Better insight into the associations between pendimethalin use and the histologic specificity for both lung cancer and rectal cancer from continued follow-up of this cohort would be valuable. Finally, we are

unable to evaluate time-dependent exposures and risk because follow-up of this cohort is relatively short (7.5 years).

This is the first study of the associations between pendimethalin exposure and cancer incidence among pesticide applicators. The association with rectal cancer was not an a priori hypothesis and results must therefore be interpreted cautiously. Nonetheless, the Agricultural Health Study is the largest study of pesticide exposure in the world with detailed information on exposure for each pesticide. Data collection was conducted before diagnosis of cancer, precluding response bias. The detailed and comprehensive information on other pesticide exposures and other risk factors such as smoking history, diet, and alcohol consumption allowed us to adjust for potential confounding factors. Finally, the ongoing follow-up of the cohort affords the opportunity to replicate the analyses on new incident cancer cases arising in the cohort.

REFERENCES

1. Engebretson J, Hall G, Hengel M, et al. Analysis of pendimethalin residues in fruit, nuts, vegetables, grass, and mint by gas chromatography. *J Agric Food Chem*. 2001;49:2198–2206.
2. Donaldson TKD, Grube A. Pesticides Industry Sales and Usage, 1998 and 1999 Market Estimates, 2002. Available at: http://www.fwjustice.org. Accessed August 2, 2005.
3. *Farm Chemicals Handbook 2001*. Willoughby, OH: Meister Publishing Co; 2001.
4. *Herbicide Handbook of the Weed Science Society of America*, 6th ed. WSSA, Champaign, IL: WSSA; 1989.
5. US Environmental Protection Agency. *R.E.D. Facts: Pendimethalin.* Washington, DC: US EPA; 1997.
6. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. *Environ Health Perspect*. 1996;104:362–369.
7. Alavanja MC, Dosemeci M, Samanic C, et al. Pesticides and lung cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol*. 2004;160:876–885.
8. Fritz A, Percy C, Jack AK. *International Classification of Diseases for Oncology*. Geneva: World Health Organization; 2000.
9. Alavanja MC, Sandler DP, McDonnell CJ, et al. Characteristics of persons who self-reported a high pesticide exposure event in the Agricultural Health Study. *Environ Res*. 1999;80:180–186.
10. Tarone RE, Alavanja MC, Zahm SH, et al. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am J Ind Med*. 1997;31:233–242.
11. Dosemeci M, Alavanja MC, Rowland AS, et al. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. *Ann Occup Hyg*. 2002;46:245–260.
12. Breslow NE, Day NE. Statistical methods in cancer research. Volume I—the analysis of case–control studies. *IARC Sci Publ*. 1980;5–338.
13. Dunkelberg H, Fuchs J, Hengstler JG, et al. Genotoxic effects of the herbicides alachlor, atrazine, pendimethalin, and simazine in mammalian cells. *Bull Environ Contam Toxicol*. 1994;52:498–504.
14. Zhong Y, Rafnsson V. Cancer incidence among Icelandic pesticide users. *Int J Epidemiol*. 1996;25:1117–1124.
15. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer*. 1985;52:259–270.
16. Forastiere F, Quercia A, Miceli M, et al. Cancer among farmers in central Italy. *Scand J Work Environ Health*. 1993;19:382–389.
17. Swaen GM, van Vliet C, Slangen JJ, et al. Cancer mortality among licensed herbicide applicators. *Scand J Work Environ Health*. 1992;18:201–204.
18. Bond GG, Wetterstroem NH, Roush GJ, et al. Cause specific mortality among employees engaged in the manufacture, formulation, or packaging of 2,4-dichlorophenoxyacetic acid and related salts. *Br J Ind Med*. 1988;45:98–105.
19. Saracci R, Kogevinas M, Bertazzi PA, et al. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet*. 1991;338:1027–1032.
20. Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med*. 1991;324:212–218.
21. Arbman G, Axelson O, Fredriksson M, et al. Do occupational factors influence the risk of colon and rectal cancer in different ways? *Cancer*. 1993;72:2543–2549.
22. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer*. 2004;108:433–442.
23. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the agricultural health study from Iowa. *Epidemiology*. 2002;13:94–99.
24. Hoppin JA, Yucel F, Dosemeci M, et al. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. *J Expo Anal Environ Epidemiol*. 2002;12:313–318.